

**REMARKS**

The Final Office Action of January 30, 2007, has been received and reviewed. The present response is submitted under 37 C.F.R. § 1.114 with a Request for Continued Examination. Claims 1-63 are currently pending in the application. Claims 11 and 18-20 were previously withdrawn from consideration. Claims 1-10, 12-17, and 21-63 are under consideration. Claims 1-10, 12-17, and 21-30 stand rejected. Claim 22 stands objected to. Claims 1-10, 12, 13, and 21-30 are amended herein. New claims 31-63 are presented herein. Basis for new claims 31-63 can be found throughout the Specification. All amendments are made without prejudice or disclaimer. No new matter has been presented. Reconsideration is respectfully requested.

**Claim Objections**

Claim 22 stands objected to as being a substantial duplicate of claim 1. Applicant notes the objection and will address the objection if either claim 22 or claim 1 becomes allowed.

**Rejections under 35 U.S.C. § 112, First Paragraph, Written Description**

Claims 21, and 23-30 stand rejected under 35 U.S.C. § 112, first paragraph as assertedly failing to comply with the written description requirement. Specifically, it was asserted that

The specification fails to define those structural features of *Lactococcus* thymidylate synthase gene(s) that are commonly possessed by members of the genus that distinguish them from others. The specification fails to provide the structure and function correlation common to all members of the genus of *Lactococcus* thymidylate synthase genes(s). Office Action mailed January 30, at page 4.

Applicant respectfully traverses the rejections as hereinafter set forth.

35 U.S.C. § 112, Paragraph 6 relates that

An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claims shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

“The USPTO must apply 35 U.S.C. 112, sixth paragraph in appropriate cases, and give claims their broadest reasonable interpretation, in light of and consistent with the written description of the invention in the application. *In re Donaldson Co.*, 16 F.3d 1189, 29 USPQ2d 1845 (Fed. Cir. 1994). Under MPEP §2181(I), a claim element will be interpreted to invoke 35 U.S.C. 112, sixth paragraph, if it meets the following 3-prong analysis:

- (A) the claim limitation must use the phrase “means for” or “step for;”
- (B) the “means for” or “step for” must be modified by functional language; and
- (C) the phrase “means for” or “step for” must not be modified by sufficient structure, material, or acts for achieving the specified function.

Claim 21 contains a means plus function element. Specifically, claim 21 recites, in part, “a means for encoding a defective thymidylate synthase gene.” Prong (A) of the 3-prong test is clearly met as the claim clearly recites “means for.” Prong (B) of the 3-prong test is also met as the means for is modified by function language, to wit: “means for encoding a defective thymidylate synthase gene.” Lastly, prong (C) of the 3-prong test is met as the “means for” recited in claim 21 is not modified by any structure, material, or acts for achieving the specified function. As such, claim 21 invokes 35 U.S.C. 112, sixth paragraph.

In rejecting claim 21, the Examiner asserts that insufficient written description is insufficient for the genus claimed. However, the Examiner’s assertion the indeterminate nature of the *Lactococcus* thymidylate synthase genes(s) is in direct contravention to 35 U.S.C. § 112, sixth paragraph. As noted above, 35 U.S.C. § 112, sixth paragraph, provides, in part, that “such claims shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.” As such, the “means” recited in claim 21 cannot be construed as covering an indeterminate genus of *Lactococcus* thymidylate synthase genes(s) as the means must be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

Further the MPEP at § 2163 (II)(3)(a) indicates that “A means- (or step) plus-function claim is adequately described under 35 U.S.C. § 112, paragraph 1, if the written description adequately links or associates adequately described particular structure, material or acts to the function recited in a means- (or step) plus function limitation.”

Applicant respectfully submits that *Lactococcus* thymidylate synthase genes(s) are adequately described in the Specification. Applicant provides numerous examples of these genes, or portions of these genes, including SEQ ID NOs, 1, 2, 3, 5, 7, 14, 15, 16, 18, and 23-32, as well as *L. lactis* ssp. *Lactis* CHCC373 by reference to GenBank acc. Number AF336368 in ¶ [0036]. Thus, applicant respectfully submits that they have met the written description requirement at least as they have pointed out no less than 19 species that fall within the claims.

In addition, it is well-known in the art that thymidylate synthase genes are highly conserved. For example, Taylor *et al.* teaches that amino acid sequence homology between thymidylate synthase from species as distant yeast, human, and *E. coli* is no less than 60% in pair-wise comparisons (J. Biol. Chem. 262:11 5298-5307. 5304, column 2).

Given such high degree of thymidylate synthase conservation between even different kingdoms (here above, fungi, animals and prokaryotes), the thymidylate synthase gene will be very highly conserved between members of the comparably narrow *Lactococcus* species. This is corroborated by the herewith enclosed sequence alignments (see attached alignment) between *thyA* nucleotide sequences from the three *Lactococcus* strains exemplified in the application, *i.e.*, *L. lactis* ssp. *cremoris* MG1363, *L. lactis* ssp. *lactis* IL1403 and *L. lactis* ssp. *lactis* CHCC373. These sequences display very high (at least 89%) sequence identity in pair-wise comparisons and even 100% sequence identity between the strains CHCC373 and IL1403. As such, applicant respectfully submits that the high degree of sequence conservation between *Lactococcus* thymidylate synthase genes allows a person of ordinary skill in the art to recognise and identify the thymidylate synthase gene from any further member of *Lactococcus* species.

In addition, as the MPEP and the Federal Circuit have pointed out, written description is satisfied if the specification adequately links a particular material to the function recited. *See In re Donaldson, supra*. Applicant submits that specification adequately links the sequences noted *supra* with the recited function as these materials are clearly noted in the Specification as useful in generating the composition of claim 21. *See, e.g.* ¶ [0028] and [0031] as well as the Examples.

For at least the foregoing reasons applicant respectfully submits that claim 21 has adequate written description requirement as the requirement is applied to means-plus-function

claims. Consequently, applicant respectfully requests withdrawal of the rejection of claim 21 under 35 U.S.C. § 112, first paragraph, for lack of written description and reconsideration of same.

In addition, applicant respectfully submits that adequate written description exists for claims 23-30, *inter alia*, as depending from adequately described claim 21. Consequently, applicant respectfully requests withdrawal of the rejection of claims 22-30 under 35 U.S.C. § 112, first paragraph, for lack of written description and reconsideration of same.

#### **Rejections under 35 U.S.C. § 112, First Paragraph, Enablement**

Claims 21, and 23-30 stand rejected under 35 U.S.C. § 112, first paragraph as assertedly failing to comply with the enablement requirement. Specifically, it was asserted that

The specification, while being enabling for a *Lactococcus* bacterium comprising a disrobed thymidylate synthase, said gene comprising SEQ ID NOS 3 or 5, does not reasonably provide enablement for a *Lactococcus* bacterium comprising a disrupted thymidylate synthase gene having an undefined percent identity to SEQ ID NOS: 3 or 5. Office Action mailed January 30, at page 5.

Applicant respectfully traverses the rejections as hereinafter set forth.

As noted *supra*, means-plus-function “claims shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.” Applicant respectfully submits that they are not required to enable a specific percentage identity to SEQ ID NOS: 3 or 5 as the means are limited to those structures, materials, or acts described in the specification and equivalents thereof. Applicant respectfully submits that those structures, materials, or acts described in the specification and equivalents are adequately enabled. Further, the Examiner has not pointed out which of the structures, materials, or acts described in the specification and equivalents are not adequately described.

In addition, it is not questioned that the application teaches to introduce a defect in a *Lactococcus* thymidylate synthase gene having a known sequence. While this is exemplified on the thymidylate synthase gene of the MG1363 strain, the application also identifies the sequences of the thymidylate synthase genes of the IL1403 and CHCC373 strains, and thus undisputedly

allows a skilled artisan to carry out the method of the invention in these latter strains.

The Examiner asserts that the application does not allow one to mutate the thymidylate synthase gene of any other *Lactococcus* strain, because the corresponding *thyA* sequences are not disclosed in the application. In addition, the Examiner asserts that such further *thyA* sequences could not be obtained by a skilled person without undue experimentation because the homology of such further *thyA* genes to those disclosed in the application would be too low for isolation by hybridisation.

In contrast to this allegation, as explained above, the homology between thymidine synthase genes of different members of the *Lactococcus* species is fairly high. Therefore, a skilled person will not experience any undue burden in isolating, *e.g.*, by means of hybridization, the thymidylate synthase gene from any further member of *Lactococcus* species. Moreover, as taught by the present application, one will be able to determine the sequences required for altering said *thyA* gene.

Furthermore, even if experimentation is required, and even if that experimentation may be difficult and time consuming, such does not mandate a conclusion that such experimentation would be considered to be undue in the art. *See, e.g. Falkner v. Inglis* 448 F.3d 1357, 1365 (Fed. Cir. 2006). In the field of microbiology, great expenditures of time and effort are ordinary and the isolation of a highly homologous sequence from a *Lactococcus* species would be neither out of the ordinary nor undue.

Consequently, when armed with the teachings of the present application, a skilled person will be able to introduce a defect into the thymidylate synthase gene of any member of the *Lactococcus* species. Hence, claims 21 *et seq.* are enabled.

For at least the foregoing reasons applicant respectfully submits that claim 21 is enabled as the requirement is applied to means-plus-function claims. Consequently, applicant respectfully requests withdrawal of the rejection of claim 21 under 35 U.S.C. § 112, first paragraph, for lack of enablement and reconsideration of same.

In addition, applicant respectfully submits that adequate enablement exists for claims 23-30, *inter alia*, as depending from enabled claim 21. Consequently, applicant respectfully

requests withdrawal of the rejection of claims 22-30 under 35 U.S.C. § 112, first paragraph, for lack of enablement and reconsideration of same.

**Rejections under 35 U.S.C. § 112, Second Paragraph**

**Claims 1-10 and 12-17**

Claims 1-10 and 12-17 stand rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite. Specifically, it was asserted that “[t]he claims are confusing because ‘said gene’ is a defective gene whereas SEQ ID NOs: 3 and 5 are sequences of the endogenous non-defective genes.” Office Action mailed January 30, 2007, at page 6. Applicant respectfully traverses the rejections as herein after set forth

Although the applicant does not agree that any of the claims are indefinite, to expedite prosecution, claims 1, 5, and 12 have been amended herein. Specifically, claims 1, 5, and 12 have been amended to no longer recite “wherein said thymidylate synthase genes is selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:5.” Consequently, applicant submits that claim 1, 5, and 12, as amended, can no longer be rejected as being indefinite for the recitation of the above phrase. As such, applicant respectfully requests the withdrawal of the rejections of claims 1, 5, and 12 under 35 U.S.C. § 112, second paragraph, and reconsideration of same.

In addition, applicant respectfully submits that claims 2-4, 6-10, and 13-17 are not indefinite, *inter alia*, as these depend from definite claims 1, 5, and 12. As such, applicant respectfully requests the withdrawal of the rejections of claims 2-4, 6-10, and 13-17 under 35 U.S.C. § 112, second paragraph, and reconsideration of same.

**Claim 21**

Claim 21 stands rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite for various reasons. Applicant respectfully traverses the rejections as hereinafter set forth.

Claim 21 stands rejected 35 U.S.C. § 112, second paragraph, for reciting “a genome.” The Examiner notes that every bacterium comprises a genome. Office Action mailed January 30, at page 7. Applicant notes that most bacteria comprise a genome, unless that genome has been

removed. However, applicant is unsure how the recitation of “a genome” makes claim 21 unclear as one of ordinary skill in the art understands what is meant by a genome.

Claim 21 stands rejected 35 U.S.C. § 112, second paragraph, assertedly as the metes and bounds of “a means” is not defined in specification are not clear. Office Action mailed January 30, at page 7. As noted *supra*, means-plus-function “claims shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.” As such, applicant respectfully submits that the metes and bounds of “a means” is provided by 35 U.S.C. § 112, paragraph six, to wit: the corresponding structure, material, or acts described in the specification and equivalents thereof.

Claim 21 stands rejected 35 U.S.C. § 112, second paragraph, for reciting “wherein said genome has been genetically modified in comparison to wild-type *Lactococcus*.” Office Action mailed January 30, at page 7. Although the applicant does not agree that any of the claims are indefinite, to expedite prosecution, claim 21 has been amended herein. Specifically, claim 21 has been amended to no longer recite “wherein said genome has been genetically modified in comparison to wild-type *Lactococcus*.” Consequently, applicant submits that claim 21, as amended, can no longer be rejected as being indefinite for the recitation of the above phrase.

In view of the foregoing, applicant respectfully requests the withdrawal of the rejections of claim 21 under 35 U.S.C § 112, second paragraph, and reconsideration of same.

Claim 22

Claim 22 stands rejected 35 U.S.C. § 112, second paragraph, for reciting “wherein the means for encoding a defective thymidylate synthase gene comprises a thymidylate synthase gene selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:5.” Office Action mailed January 30, at page 7. Although the applicant does not agree that any of the claims are indefinite, to expedite prosecution, claim 22 has been amended herein. Specifically, claim 22 has been amended to no longer recite “wherein the means for encoding a defective thymidylate synthase gene comprises a thymidylate synthase gene selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:5.” Consequently, applicant submits that claim 22, as amended, can no longer be rejected as being indefinite for the recitation of the above phrase.

In view of the foregoing, applicant respectfully requests the withdrawal of the rejections of claim 22 under 35 U.S.C § 112, second paragraph, and reconsideration of same.

**Rejections under 35 U.S.C. § 103**

Claims 21 and 23-30 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Steidler *et al.* (Nature Biotechnology 21:7 785-789) (hereinafter “Steidler”) in view of Taylor *et al.* (J. Biol. Chem. 262:11 5298-5307) (hereafter Taylor). Specifically, it was asserted that a skilled person would have been motivated to produce a *L. lactis* strain comprising a disrupted thymidylate synthase gene, because he would expect that such strain could deliver a drug to a patient without contaminating the outside environment where thymidine/thymine is not present in sufficient amounts. Office Action mailed January 30, at page 8. Applicant respectfully traverses the rejections as hereinafter set forth.

Applicant respectfully submits, even if it is assumed, *arguendo*, that a skilled person could have concluded from Taylor (who, however, only describes yeast) that *thyA* defective *L. lactis* would not survive in outside environment, the skilled artisan would not expect such *L. lactis* to effectively deliver drugs when administered.

Namely, when *L. lactis* is administered as in Steidler, it passes the gut where the levels of thymidine/thymine are minimal or non-existent. Thus, the skilled person would expect that *thyA* defective *Lactococcus* would not be viable in the gut and therefore could not deliver drugs thereto. Clearly, Taylor cannot alter this conclusion, since Taylor does not at all address the fate of *thyA* deficient yeast in the gut.

As such, applicant submits that a skilled person would not have expected *thyA* defective *Lactococcus* to survive in and deliver drugs to patients and therefore would not find it obvious to modify the *Lactococcus* of Steidler with the *thyA* deficiency of Taylor, let alone to further modify such *thyA* deficient *Lactococcus* to express prophylactic or therapeutic molecules.

In contrast, it is only the surprising realisation by the present inventor that the viability of *thyA* defective *Lactococcus* in the gut is sufficiently high compared to control strains that motivates the skilled artisan to prepare the above *thyA* defective *Lactococcus*.

Moreover, even if a skilled person were motivated to prepare *thyA* defective *Lactococcus*

(*quod non*), there existed no reasonable expectation of success in doing so.

In particular, it asserted that *thyA* mutants can be isolated from “bacteria,” only the example of *Rhizobium meliloti* is mentioned. Office Action mailed January 30, at page 10. However, the rejection is entirely silent about the feasibility of isolating *thyA* defective mutants of *Lactococcus*.

In fact, the art teaches away from the isolation of *thyA*-deficient strains. For example, Steidler *et al.* notes: “researchers were unable to isolate *thyA*-deficient strains by use of conventional selection methods” (Steidler at p. 788, col. 1, l. 8-11), which shows that conventional attempts to inactivate the essential *thyA* gene failed.

In addition, there is no reasonable expectation of success as a person skilled in the art would also not expect success from using the homologous recombination of Taylor to construct *thyA* deficient *Lactococcus*. In particular, Taylor only relates to *S. cerevisiae* in which homologous recombination is relatively efficient, while it is not efficient in *Lactococcus*.

Hence, given the low, if any, occurrence of homologous recombination in *Lactococcus*, coupled with the strong selection pressure against *thyA* inactivation, one would not expect any success from this approach in *Lactococcus*. The expectation of failure would be even more pronounced for growth restricted *thyA* mutants obtainable herein by double homologous recombination.

In conclusion, the prior art provides no teaching that would guarantee a reasonable success for a skilled person in generating a *thyA* mutant of *Lactococcus*, even if he were motivated to do so (*quod non*). Thus the prior art lacks motivation, lacks a reasonable expectation of success, and fails to teach all elements of the claims.

In view of the foregoing, applicant respectfully submits that claim 21 cannot be obvious over Steidler in view of Taylor. Consequently, applicant respectfully requests the withdrawal of the rejection of claim 21 under 35 U.S.C. § 103(a) and reconsideration of same.

In addition, applicant respectfully submits that claims 23-30 are non-obvious, *inter alia*, as depending from non-obvious claim 21. Consequently, applicant respectfully requests the withdrawal of the rejections of claims 23-30 under 35 U.S.C. § 103(a) and reconsideration of same.

**CONCLUSION**

In light of the above amendments and remarks, applicant respectfully requests reconsideration of the application. If questions remain after consideration of the foregoing, or if the Office should determine that there are additional issues which might be resolved by a telephone conference, the Office is kindly requested to contact applicant's attorney at the address or telephone number given herein.

Respectfully submitted,



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## ANNEX - *Lactococcus thyA* sequence alignments

thyA MG1363 vs thyA IL1403: 89% identical

thvA MG1363 vs thvA CHCC373: 89% identical

thyA CHCC373 vs thyA IL1403: 100% identical